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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,243	01/04/2002	Paul I. Freimuth	BSA 01-22	6646

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EXAMINER
MITCHELL, LAURA MCGILLEM

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/037,243	FREIMUTH ET AL.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64, 99-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64 and 99-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claim 64 has been amended, claims 1-63 and 65-98 are cancelled and claims 99-100 have been added in the amendment filed 7/16/2007. Claims 64 and 99-100 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64, 93 and 95-98 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 93 has been canceled; therefore the rejections of claims 93 and 95-98 are mooted. Claim 64 has been amended to correct the indefiniteness of the limitation regarding the multiple cloning site and the insertion of the second sequence. The rejection of claim 64 under 35 U.S.C. 112, second paragraph, as being indefinite has been withdrawn.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64 and 99-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 93 has been canceled; therefore the rejections of claims 93 and 95-98 are mooted. Claims 99-100 are newly added to this rejection.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 5/5/2006 and for reasons outlined below.

Applicants have amended claim 64 to limit the vector optimized for use in all protozoans to *E. coli* cells. New claim 99 is limited to an "*E. coli* expression vector" and new claim 100 is limited to an "expression vector optimized for use in bacterial cells.., where the bacterial cells are selected from the group consisting of *E. coli, B. subtilis*, and *R. eutrophus*.

Applicants point out that the group of bacterial cells of new claim 100 are those for which pET-type vectors and T7 gene expression systems have been developed and which are known to those of ordinary skill in the art. The Applicant draws the Examiner's attention to the references to T7 expression systems in *B. subtilis*: Conrad, B., et al. (1996) Mol. Gen. Genet. 250:230-236 and in *R. eutrophus*: Barnard, G.C., et al. (2004) Prot. Exp. & Purif. 38:264-271. Applicants submit that they have amended the claims to delete the phrase "consisting essentially of" that caused the claim to encompass a large genus of vectors. Applicants submit that the expression of the first and second nucleic

acid sequences yields a fusion protein consisting of the peptide extension fused to the carboxyl-terminus of the protein or polypeptide of interest in all claims presently under examination.

Applicant's arguments filed 7/26/2007 have been fully considered but they are not persuasive. Applicants claim an expression vector optimized for use in *E.coli* cells comprising a first nucleic acid sequence encoding a peptide extension that is Peptide T7B (SEQ ID NO:6), an MCS in which a second in frame nucleic acid sequence encoding a peptide of interest is inserted. Applicants also claim an *E.coli* expression vector comprising a first nucleic acid sequence encoding a peptide extension that is Peptide T7B (SEQ ID NO:6) and an MCS in which a second in frame nucleic acid sequence encoding a peptide of interest is inserted (claim 99). Applicants claim an expression vector optimized for use in bacterial cells that are *E. coli, B. subtilis*, and *R. eutrophus* cells comprising a first nucleic acid sequence encoding a peptide extension that is Peptide T7B (SEQ ID NO:6) and an MCS in which a second in frame nucleic acid sequence encoding a peptide of interest is inserted (claim 100).

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

In the instant case, the specification discloses one expression vector optimized for use in *E.coli* cells. The disclosed example vector is pET15. The specification discloses that the bacteriophage T7-based expression system is a powerful prokaryotic system where a gene of interest is cloned downstream of a promoter element that is derived from the bacteriophage T7 DNA genome. The specification also discloses that an expression vector should have all the elements that are required for the *in vivo* transcription and translation of a protein of interest by a host cell (see paragraph 0028). There is no other disclosure regarding how the claimed expression vector would be optimized for use in *E.coli* cells or bacterial cells that are *E. coli, B. subtilis*, and *R. eutrophus* cells.

The claimed vector comprises a first nucleic acid sequence encoding a peptide extension with the function of "enhancing the solubility and proper folding of a protein or polypeptide of interest". The claimed vector also comprises a sequence encoding a protein or polypeptide of interest with a first nucleic acid sequence encoding a peptide extension. The claims are specifically limited to a vector with a peptide extension that is Peptide T7B, which is a 57-residue polypeptide that has the ability to enhance solubility and biological activity of a protein of interest when expressed as a fusion protein. The specification discloses variations of the peptide with amino acid substitutions, but which all maintain a net negative charge of between –2 and –20. However, the instant specification has not described any other vector besides the pET15 vector that would have the function of being optimized for use in *E. coli, B. subtilis*, and *R. eutrophus* cells

and would include a sequence for a peptide extension with the claimed function of enhancing solubility and folding of a fused protein of interest.

The claimed vector encodes a very large genus of any sequence encoding a protein or polypeptide. The claims do not specifically limit the protein of interest to one that requires folding or that has a problem with insolubility when recombinantly produced. The specification discloses and exemplifies a protein of interest that is a coxsackie and adenovirus receptor (CAR) D1 domain. The exemplified vector pET15 comprises CAR D1 fused to T7B at the carboxyl terminus. Through experimentation disclosed in the specification, Applicants determine that the peptide extension functions to increase solubility of a protein of interest is the net negative charge carried by the extension and by not formation of amphiphilic α-helices or recruitment of chaperone proteins. However, the specification discloses that the T7B peptide does not universally promote protein folding *in vivo* (see paragraph 0080) demonstrated in an experiment in which the distal domain of human A33 protein is used as the protein of interest in the expression vector. The A33 protein is structurally similar to the CAR D1 protein but extension of the carboxyl terminus of A33 D1 with T7B did not increase solubility of A33. Applicants also attached a variation of the T7B to A33 D1 and concluded that although a peptide extension was able to partially solubilize A33 D1, it may not be able to mediate proper folding of the domain.

There is no description of how the structure of the disclosed vector pET15 comprising CAR D1 T7B relates to the structure of the claimed expression vector comprising a sequence encoding any protein of interest fused to a T7B peptide

extension. There are many known and available expression vectors for use in *E. coli*. From the instant disclosure, the skilled artisan cannot envision all expression vectors optimized for use in *E. coli, B. subtilis*, and *R. eutrophus* cells that encode any polypeptide or protein of interest that is substantially insoluble or biologically inactive and the solubility and folding of which would be enhanced by fusion of a peptide T7B at the carboxyl terminus. The specification does not disclose what particular promoters or regulatory sequences that would be present on the claimed vector that might act to enhance or repress the expression of the peptide of interest, and which would effect the function of the expression vector (i.e. to produce the fusion polypeptide of interest). The specification does not disclose any other vector that has been optimized for use in *E. coli, B. subtilis*, and *R. eutrophus* cells besides a vector that would comprise a promoter element derived from bacteriophage T7 genome. The genus of expression would be expected to have divergent functional properties as changes in the polypeptide of interest and vector components can have significant effects on the structure and properties of the expression vector. The applicant does not provide an indication of how the sequence of pET15 CAR D1 T7B is representative of other expression vectors comprising T7B that would enhance the solubility and proper folding of any protein of interest. The common attributes of the optimized expression vector comprising T7B are not described and the identifying attributes of the individual vectors comprising a sequence of protein of interest that requires enhancement of folding and solubility are not described. Therefore, there is no structural and functional basis provided by the prior art or the specification for one of ordinary skill in the art to envision all *E.coli*

expression vectors as claimed. According to these facts, one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variant of the genus and is insufficient to support them.

Applicant's arguments, see REMARKS, and amendments filed 7/16/2007, with respect to claim 64 have been fully considered and are persuasive. Claim 93 has been canceled; therefore the rejections of claims 93 and 95-98 under 35 USC § 112, first paragraph are moot. Applicants have amended the claim 64 to delete the phrase "consisting essentially of" and narrowed the limitation regarding the cells for which the vector will be used to *E. coli.* New claims 99-100 are drawn to vectors for use in *E. coli, B. subtilis*, and *R. eutrophus*. The rejection of claim 64 under 35 USC § 112, first paragraph (enablement) has been withdrawn.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell, PhD
Examiner
9/25/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER